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**Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.**

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## **1.0 PROTOCOL SUMMARY AND/OR SCHEMA**

**Title .** A PHASE II STUDY OF ATEZOLIZUMAB IN RELAPSED OR REFRACTORY HODGKIN LYMPHOMA

**Objectives:** The main objectives is to determine the 12 month progression-free survival of atezolizumab in relapsed/refractory HL patients who are anti-PD-1 previously treated and relapsed/refractory (R/R) HL patients who are anti-PD-1 treatment naïve.

**Patient Population:** Patients with relapsed or refractory Hodgkin's lymphoma who had previous PD-1 therapy (cohort 1) and R/R HL patients who are anti-PD-1 treatment naïve (cohort 2).

**Study Design:** This is a protocol comprised of a single institution phase II study in HL evaluating the efficacy of atezolizumab.

**Treatment Plan:** Following enrollment, patients will be assigned to receive therapy with Atezolizumab (1200mg) given intravenously every 3 weeks according to the dosing schedule described in the protocol. Patients will accrue in a two stage design and monitored for safety of Atezolizumab, complete response rate, progression free survival and correlative biomarkers.

**Time to Completion:** A maximum of 57 patients will be treated with atezolizumab. The study will enroll 25 patients in cohort 1 and 32 patients in cohort 2. To reach this goal, we anticipate enrolling 2 patients per month in cohort 1 and 3 patients per month in cohort 2.

## **2.0 OBJECTIVES AND SCIENTIFIC AIMS**

### **Primary Objectives**

Determine the 12 month progression-free survival of atezolizumab in relapsed/refractory HL patients who are anti-PD-1 previously treated (cohort 1) and relapsed/refractory HL patients who are anti-PD-1 treatment naïve (cohort 2).

### **Secondary Objectives**

1. Determine the disease control rate, overall response rate, complete response rate, duration of response of atezolizumab, and progression free survival of atezolizumab in relapsed/refractory HL patients who are anti-PD-1 previously treated (cohort 1) and in relapsed/refractory HL patients who are treatment naïve (cohort 2).
2. To determine whether pre-treatment tumor expression of MHC-I, MHC-II, PD-L1, or PD-L2, the effector to regulatory T cell ratio at baseline or in response to therapy, changes in expression of T-cell extrinsic apoptosis-related markers FasL and TRAIL, or PI3K activation on HRS cells at baseline or in response to therapy predicts treatment response.
3. To determine the safety and toxicity of atezolizumab in patients with relapsed and refractory Hodgkin lymphoma.

## **3.0 BACKGROUND AND RATIONALE**

### **3.1 Hodgkin Lymphoma**

Classical Hodgkin lymphoma (HL) is an aggressive B-cell lymphoma with an annual incidence of fewer than ten thousand cases per year [8]. It is primarily a disease of younger individuals with the majority of patients diagnosed between the age of 15 and 30. HL is a curable disease in all untreated patients with chemotherapy and/or radiation. However, up to one third of patients relapse following standard therapy [9-11]. For these patients, the standard of care is salvage chemotherapy followed by autologous stem cell transplantation; however,

this carries a high risk of treatment-related morbidity and some risk of transplant-associated mortality. Additionally, this strategy is curative only in about one half of patients who relapse [12, 13]. The majority of patients with disease that persists or recurs after salvage autologous stemcell transplantation ultimately succumb to their disease; the only curative option in this setting is allogeneic transplantation which is associated with high rates of transplant associated morbidity and mortality and is only able to achieve long-term remissions in a fraction of patients [14, 15].

### **3.2 Immunotherapeutic strategies in HL and a role for the PD-1/PD-L1 axis**

One exciting prospect for therapeutic intervention in HL is via targeting of the costimulatory receptor Programmed Cell Death-1 (PD-1; CD279), a cell surface signaling molecule that delivers inhibitory signals that regulate the balance between T cell activation and tolerance by interacting with its ligands, PD-L1 (CD274; B7-H1) and PD-L2 (B7-DC/CD273). PD-1 is a 55 kD type I transmembrane protein that is a member of the CD28 family of T-cell costimulatory receptors, which also includes CTLA-4, ICOS, and BTLA [34]. PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells [35] and is upregulated on many tumor-infiltrating lymphocytes [36]. Binding of either PD-1 ligand to PD-1 suppresses T-cell activation in both murine and human systems [40]. In response to ligand binding, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of TCR-proximal signaling molecules required for T cell activation such as CD3 $\zeta$ , PKC $\theta$  and ZAP-70 [41-43]. Expression of either PD-1 ligand is thought to occur in healthy individuals in response to chronic antigenic stimulation in order to limit T-cell mediated damage to end-organs; indeed, PD-1 mediated suppression of T cell responses was initially described in murine models of chronic viral infection, a phenomenon known as T-cell “exhaustion” [44].

Recently, malignant co-opting of this regulatory pathway has been described via constitutive expression of PD-1 ligands in HL. A recent integrative analysis reveals selective 9p24.1 amplification, which includes the PD-L1 and PD-L2 loci, increased PD-L1 expression, and further induction via JAK2 in nodular sclerosing HL [26, 48]. Even in patients without genetic amplifications of PD-L1 or PD-L2, physiologic upregulation of these ligands likely occurs downstream of JAK/STAT signaling, IFN $\gamma$  production or, in EBV-associated cases of cHL, expression of the viral-associated protein LMP-1 [49, 50].

These findings suggested that the PD-1/PD-L1 pathway plays a critical role in HL immune evasion and should be considered as an attractive target for therapeutic intervention. Indeed, blockade of PD-1 increases the sensitivity of T cells to foreign antigens and increases effector function and cytokine production of both CD4 and CD8 T cells in both models of both tumor and virally mediated chronic T cell exhaustion [44, 56, 57]. Furthermore, in lymphomas, PD-1 expressing tumor infiltrating lymphocytes have impaired cytokine responses to antigenic stimulation that can be reversed by blockade of PD-1, leading to an increase in IL-2 and IFN- $\gamma$  production, an upregulation in expression profiles suggestive of NK and cytotoxic T cell activity, and ultimately tumor rejection [54]. This correlative data provided a strong rationale for targeting PD-1/PD-L1 interaction in lymphoma.

### **3.3 Clinical activity of anti-PD-1 therapy**

In HL, anti-PD-1 therapy has resulted in impressive and durable remissions in patients with highly refractory disease. Both pembrolizumab and nivolumab, monoclonal antibodies targeted at PD-1 on tumor-infiltrating T-cells, elicited overall response rates of 60-70%, with many remissions lasting greater than one year. Despite this encouraging activity, a number of outstanding issues remain with respect to blockade of the PD-1/PD-L1 axis. Complete remission to both pembrolizumab and nivolumab remain rare (<20%) and the duration of response remains less than one year, with more than half of patients progressing at 12 months.

The optimal method for targeting the PD-1 pathway in HL remains unknown. Despite the high activity of anti-PD-1 therapy in HL, PD-1 expression within the HL microenvironment is often low to absent.<sup>9</sup> On the contrary, PD-L1 is almost universally expressed on the RS cells of HL tumors, and the extent of PD-L1 amplification in HL correlates with prognosis. Direct targeting of PD-L1, rather than PD-1, may more profoundly promote anti-tumor immune responses in HL. It may also more effectively silence any pro-survival signals transmitted to HL Reed Sternberg cells through PD-L1 ligation. In this manner we hypothesize that targeting PD-L1 may be more effective than anti-PD-1 therapy in HL and potentially overcome resistance to anti-PD-1 therapy. It should be noted that PD-L2 expression on RS cells has been described; it is possible that engagement of PD-L2 to PD-1 will counteract the impact of PD-L1 blockade and thus reduce efficacy of anti-PD-L1 therapy. We will evaluate for this possibility by assessing PD-L1, PD-L2, and PD-1 expression within patients' tumor samples and correlating expression with response.

Furthermore, the mechanism by which impairing the PD-L1/PD-1 interaction in HL promotes anti-tumor responses remains enigmatic. In solid tumors, blocking



this interaction results in enhanced CD8 T cell-dependent immune responses. However, HL is characterized by a very high prevalence of mutations in the beta-2-microglobulin gene, resulting in constitutive loss of major histone compatibility complex class-1 (MHC-1) expression on RS cells, which should eliminate any CD8 T-cell anti-tumor responses. We will evaluate how anti-PD-L1 therapy affects anti-tumor responses in cHL through immunohistochemical, flow cytometry, and high-throughput T cell receptor sequencing studies performed on biopsies obtained prior to and on therapy and correlating with clinical response.

Several anti-PD-L1 agents are in development and have demonstrated significant activity in melanoma, non-small cell lung cancer, renal cell carcinoma, and bladder cancer; but they have not been evaluated in HL. Atezolizumab, a humanized IgG<sub>1</sub> anti-PD-L1 monoclonal antibody, has already demonstrated safety and efficacy in multiple tumor types. We propose a phase II study evaluating atezolizumab in both anti-PD-1 resistant and naïve patients with rel/ref HL.

## **4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION**

### **4.1 Design**

We will aim to enroll 2 cohorts of patients. Initially, we will open cohort 1, which will include patients with previous anti-PD-1 therapy. Should cohort 1 not meet criteria for early stopping at the end of the first stage, we will open a second cohort which will include patients who never received anti-PD-1 therapy. Eligible patients will receive atezolizumab IV every 3 weeks. Patient will undergo disease assessment with PET/CT every 3 cycles for the first 12 cycles and subsequently every 4 cycles. Treatment may continue for up to 2 years.

### POPULATION AND SAMPLE

Patients aged 18 and older with rel/ref HL who have failed or been deemed ineligible for autologous stem cell transplant and who have received prior Brentuximab vedotin will be enrolled. Patients must have measurable disease (according to RECIL Criteria) prior to enrolling on study.

### TRIAL SCHEMA

Patients will receive treatment on study once every 3 weeks and response assessment with PET scans will be performed every 3 cycles for the first 12 cycles and subsequently every 4 cycles. Treatment may continue for up to 2 years.

### CLINICAL PRACTICE

Patients will be seen and evaluated at MSK outpatient lymphoma clinics. Infusion of treatment will be performed as per MSK standard practice at MSK.

## TREATMENT REGIMEN

Atezolizumab 1200 mg IV every 3 weeks

### **4.2 Intervention**

Treatment will be Atezolizumab administered at 1200 mg IV every 3 weeks. A cycle is defined as 3 weeks of therapy. Therapy will continue until disease progression, intolerable toxicities or death for a maximum duration of treatment of 36 cycles.

## **5.0 THERAPEUTIC/DIAGNOSTIC AGENTS**

### **5.1 Background on Atezolizumab**

Atezolizumab is a human immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human programmed death-ligand 1 (PD-L1) and inhibits its interaction with its receptor, programmed death-1 (PD-1). Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells.

#### **5.1.1 Formulation**

The Atezolizumab drug product is provided in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of Atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The Atezolizumab drug product is formulated as 60 mg/mL Atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

Atezolizumab must be refrigerated at 2°C – 8°C (36°F – 46°F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the ATEZOLIZUMAB drug product; therefore, each vial is intended for single use only. Discard any unused portion of drug left in a vial. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

For further details, see the Atezolizumab Investigator's Brochure.

### **5.1.2 Dosage, Administration, and Storage**

The dose level of Atezolizumab to be tested in this study is 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) administered by IV infusion every 3 weeks (21 [ $\pm$  2] days). Atezolizumab will be delivered in infusion bags with IV infusion lines that have product contacting surfaces of polyvinyl chloride (PVC) or polyolefin and 0.2  $\mu$ m in-line filters (filter membrane of polyethersulfone [PES]). No incompatibilities have been observed between Atezolizumab and PVC or polyolefin infusion materials (bags or infusion lines).

Administration of Atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

The initial dose of Atezolizumab will be delivered over 60 ( $\pm$  15) minutes. If the first infusion is tolerated without infusion-associated AEs, the second infusion may be delivered over 30 ( $\pm$  10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 ( $\pm$  10) minutes. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [ $\pm$  5] minutes), and 30 ( $\pm$  10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before and within 30 minutes after the infusion. Vital signs should be collected during the infusion only if clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

No premedication will be allowed for the first dose of Atezolizumab.

Premedication may be administered for Cycles  $\geq$  2 at the discretion of the treating physician. The management of IRRs will be according to severity as follows:

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) IRR, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.

- In the event that a patient experiences a moderate IRR (NCI CTC AE Grade 2) or flushing, fever, or throat pain, the infusion should be immediately interrupted and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the IRR.
- For severe or life-threatening IRRs (NCI CTC AE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life-threatening IRRs will not receive further infusion and will be further managed as clinically indicated until the event resolves.

Guidelines for dosage modification, treatment interruption, or discontinuation and the management of specific adverse events are provided below sections.

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the screening evaluation and the treatment discontinuation visit.

### **5.1.3 Concomitant and Excluded Therapies**

#### **5.1.3.1 Concomitant Therapy**

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or cimetidine or another H<sub>2</sub> receptor antagonist, as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and  $\beta_2$ -adrenergic agonists).

Systemic corticosteroids and TNF $\alpha$  inhibitors may attenuate potential beneficial immunologic effects of treatment with Atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles  $\geq 2$  at the discretion of the treating physician. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megastrol administered as appetite stimulant is acceptable while the patient is enrolled in the study.

Patients who use oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low-molecular-weight heparin or

warfarin at a stable dose level), or other allowed maintenance therapies should continue their use. Males and females of reproductive potential should use highly effective means of contraception.

#### **5.1.3.2 Excluded Therapy**

Any concomitant therapy intended for the treatment of cancer, whether health authority-approved or experimental, is prohibited. This includes but is not limited to the following:

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy.
- After Cycle 1, certain forms of radiotherapy may be considered for pain palliation if patients are deriving benefit (e.g., treatment of known bony metastases); Atezolizumab administration may be suspended during radiotherapy.

It is strongly recommended that:

- Traditional herbal medicines not be administered because the ingredients of many herbal medicines are not fully studied and their use may result in unanticipated drug-drug interactions that may cause, or confound assessment of, toxicity.

Patients are not allowed to receive immunostimulatory agents, including but not limited to IFN- $\alpha$ , IFN- $\gamma$ , or IL-2, during the entire study. These agents, in combination with Atezolizumab, could potentially increase the risk for autoimmune conditions.

Patients should also not be receiving immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of Atezolizumab.

Systemic corticosteroids and anti-TNF $\alpha$  agents may attenuate potential beneficial immunologic effects of treatment with ATEZOLIZUMAB but may be administered at the discretion of the treating physician. If feasible, alternatives to these agents should be considered.

In addition, all patients (including those who discontinue the study early) should not receive other immunostimulatory agents for 10 weeks after the last dose of Atezolizumab.

## **5.2 Summary of Nonclinical Experience**

The nonclinical strategy of the Atezolizumab program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetic (PK) behavior, to demonstrate an acceptable safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were thus undertaken with ATEZO LIZUMAB.

The safety, pharmacokinetics, and toxicokinetics of Atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of Atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of Atezolizumab.

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for Atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of down-modulating the PD-L1/PD-1 pathway and supported entry into clinical trials in patients.

## **5.3 Clinical Experience with Atezolizumab**

### **5.3.1 Ongoing Clinical Studies**

Current studies of Atezolizumab include one ongoing Phase Ia monotherapy study, three ongoing combination studies, five Phase II studies, and one Phase III study. Details of all ongoing studies can be found in the Atezolizumab Investigator's Brochure.

### **5.3.2 Clinical Safety**

The presented safety data for Atezolizumab have been derived mainly from the treatment of patients in Phase Ia Study PCD4989g. As of 10 May 2014, Atezolizumab has been administered to approximately 775 patients with solid and hematologic malignancies. No dose-limiting toxicities (DLTs) have been observed at any dose level, and no maximum tolerated dose (MTD) was established. Fatigue was the most frequently reported adverse event (AE).

### **Adverse Events**

The following safety data are from PCD4989g, in which Atezolizumab is being used as single-agent therapy in patients with locally advanced or metastatic solid tumors or hematologic malignancies. In 412 treated patients, 97.1% reported an AE while on study. Of these AEs, 48.8% were Grade 1 or 2 in maximum severity on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). The most frequently observed AEs (occurring in  $\geq 10\%$  of treated patients) included fatigue, nausea, decreased appetite, pyrexia, dyspnea, diarrhea, constipation, cough, headache, back pain, vomiting, anemia, arthralgia, rash, insomnia, asthenia, abdominal pain, chills, pruritus, and upper respiratory tract infection.

Grade  $\geq 3$  AEs were reported by 199 of 412 patients (48.3%). There were 51 patients (12.4%) who reported Grade  $\geq 3$  AEs that were assessed as related to study drug by the investigators. The most frequently reported related Grade  $\geq 3$  AEs included fatigue (5 patients [1.2%]), increased ALT and increased AST (each reported in 4 patients [1.0%]); and asthenia, autoimmune hepatitis, and hypoxia (each reported in 3 patients [0.7%]).

### **Immune-Related Adverse Events**

Given the mechanism of action of Atezolizumab, events associated with inflammation and/or immune-mediated AEs have been closely monitored during the ATEZOLIZUMAB clinical program. These include potential dermatologic, hepatic, endocrine, and respiratory events as well as events of hepatitis/elevated liver function tests (LFTs) and influenza-like illness. Expected adverse drug reactions associated with Atezolizumab include the following: hepatitis/transaminitis, hypothyroidism, infusion-related reactions (IRRs), pneumonitis, influenza-like illness, and dermatologic reactions. Potential adverse drug reactions include the following: anti-therapeutic antibodies (ATAs), colitis, endocrine disorders, hypersensitivity, neurologic disorders, and pericardial effusion.

**For further details, see the Atezolizumab Investigator's Brochure.**

### **5.3.3 Clinical Activity**

#### **Efficacy in Urothelial Bladder Cancer Patients**

Recently, a single-arm, multicenter phase 2 trial of atezolizumab in locally advanced and metastatic urothelial carcinoma who have progressed on platinum-based chemotherapy showed a 15% overall response rate, with durable ongoing responses in 84% of patients initially responding to treatment at a median follow-up of 11.7 months (Rosenberg JE Lancet 2016). Increased PD-L1 expression by IHC was associated in higher rates of response. Based on these results, the FDA has approved atezolizumab for metastatic urothelial carcinoma that has progressed on platinum-based chemotherapy.

## **Efficacy in Non-Small Cell Lung Cancer Patients**

Atezolizumab was compared to docetaxel in patients with previously treated advanced or metastatic non-small cell lung cancer in a multicenter, open-label phase 2 randomized controlled trial (POPLAR) (Fehrenbacher Lancet 2016). Atezolizumab was found to improve overall survival (12.6 vs. 9.7 months) compared to docetaxel. Similar to what was seen in urothelial carcinoma, more favorable responses were seen in patients with high tumor expression of PD-L1 as well as high baseline effector T-cell/interferon-gamma associated gene expression in pre-treatment samples.

### **5.4 Clinical Pharmacokinetics and Immunogenicity**

On the basis of available preliminary PK data (0.03–20 mg/kg), Atezolizumab appeared to show linear pharmacokinetics at doses  $\geq 1$  mg/kg. For the 1-mg/kg and 20-mg/kg dose groups, the mean clearance (CL) and the mean volume at steady state ( $V_{ss}$ ) had a range of 3.20–4.43 mL/kg and 48.1–64.1 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

The development of ATAs has been observed in patients in all dose cohorts and was associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). The development of detectable ATAs has not had a significant impact on pharmacokinetics for doses from 10–20 mg/kg. Patients dosed at the 10-, 15-, and 20-mg/kg dose levels have maintained the expected target trough levels of drug despite the detection of ATAs. To date, no clear relationship between detection of ATAs and AEs or IRRs has been observed.

## **6.0 CRITERIA FOR SUBJECT ELIGIBILITY**

Describe the characteristics of the patient/subject population.

### **6.1 Subject Inclusion Criteria**

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF)
- Ability and willingness to comply with the requirements of the study protocol
- Age  $\geq 18$  years.
- Patient has histologically confirmed diagnosis of Hodgkin lymphoma
- Patients must have received at least 2 prior regimens and have received or be deemed ineligible for autologous stem cell transplant, and must have received prior brentuximab vedotin.



- Patients who received prior anti-PD-1 therapy are eligible for cohort 1 only and patients who have not received prior anti-PD-1 therapy are eligible for cohort 2 only.
- Patient has at least one measurable nodal lesion ( $\geq 2$  cm) according to RECIL Criteria
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment (Cycle 1, Day 1):
  - $ANC \geq 1500$  cells/ $\mu$ L
  - WBC counts  $> 2500/\mu$ L
  - Lymphocyte count  $\geq 300/\mu$ L
  - Hemoglobin  $\geq 9.0$  g/dL
  - Total bilirubin  $\leq 1.5 \times$  upper limit of normal (ULN) with the following exception:
    - Patients with known Gilbert disease who have serum bilirubin level  $\leq 3 \times$  ULN may be enrolled.
  - AST and ALT  $\leq 3.0 \times$  ULN with the following exception:
    - Patients with liver involvement: AST and/or ALT  $\leq 5 \times$  ULN
  - Alkaline phosphatase  $\leq 2.5 \times$  ULN with the following exception:
    - Patients with documented liver involvement or bone metastases: alkaline phosphatase  $\leq 5 \times$  ULN
  - Serum creatinine  $\leq 1.5 \times$  ULN or creatinine clearance  $\geq 50$  mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:
  - $$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$
- For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use highly effective form(s) of contraception (i.e., one that results in a low failure rate [ $< 1\%$  per year] when used consistently and correctly) and to continue its use for 90 days after the last dose of Atezolizumab
- Female subject of childbearing potential should have a negative serum pregnancy within 28 days prior to receiving the first dose of study medication.

- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (see Appendix 3)

## 6.2 Subject Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry. No medical comorbidities are considered exclusions from study eligibility other than those listed below.

### General Exclusion Criteria:

- Patients who have undergone prior allogeneic transplant are excluded only if they remain on any immunosuppression or have signs or symptoms of clinical graft-versus-host disease
- Any approved anticancer therapy, including chemotherapy, hormonal therapy, or radiotherapy, within 3 weeks prior to initiation of study treatment.
- Herbal therapy (including herbal therapy intended as anticancer therapy) < 1 week prior to Cycle 1, Day 1
- AEs from prior anticancer therapy that have not resolved to Grade  $\leq$  1 except for alopecia
- Known clinically significant liver disease
- Active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease
- Pregnancy, lactation, or breastfeeding
- Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies
- Inability to comply with study and follow-up procedures
- History or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis
- Patients with a history of autoimmune hypothyroidism AND without normal thyroid hormone levels on a stable dose of thyroid replacement hormone
- Myocardial infarction or arterial thromboembolic events within 6 months prior to baseline or severe or unstable angina, New York Heart Association (NYHA) Class III or IV disease, or a QTc interval > 470 msec.
- History of Torsades de pointes, ventricular tachycardia, or ventricular fibrillation
- Uncontrolled heart failure or hypertension or uncontrolled diabetes mellitus

- Patients with uncontrolled eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations (patients without ophthalmologic involvement, rash covering <10% of the body surface area and requiring only low potency topical steroids, and without exacerbations requiring systemic therapy are eligible.)
- History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan.
- A history of radiation pneumonitis in the radiation field (fibrosis) is permitted provided that symptoms have resolved.
- Any other diseases, metabolic dysfunction, physical examination finding or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- History of HIV infection or active hepatitis B (chronic or acute) or hepatitis C infection
  - Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible.
  - Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Patients with active tuberculosis
- Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1
- Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1 for treatment of active infection (Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible)
- Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
- Major surgical procedure within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study

- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study
- Malignancies other than the disease under study within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per standard-of-care management (e.g., chronic lymphocytic leukemia Rai Stage 0, prostate cancer with Gleason score  $\leq 6$ , and prostate-specific antigen [PSA]  $\leq 10$  mg/mL, etc.)

#### **Medication-Related Exclusion Criteria:**

- Prior anti-PD-L1 therapies are excluded.
  - Patients who have received prior treatment with immunotherapy including anti-PD-1 anti-CTLA-4 may be enrolled, provided that there was no history of severe immune-related adverse effects (NCI CTCAE Grade 3 and 4)
- Treatment with investigational agent within 4 weeks prior to Cycle 1, Day 1 (or within five half-lives of the investigational product, whichever is longer)
- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1
  - Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled.
  - The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

## **7.0 RECRUITMENT PLAN**

The study will be conducted at Memorial Sloan Kettering Cancer Center. Patients will be treated by the lymphoma service at MSKCC. Every effort will be made to include women and minorities in this research study. Patients will be recruited by the treating team of physicians and medical professionals. The consenting attending physician will inform patients of their diagnosis, current treatment options, including standard treatment, and the risks, benefits, and experimental nature of this treatment program. All patients will be required to sign a statement of informed consent that conforms to FDA and IRB

guidelines. Written consent will be obtained by individual specified in section 18. Registration of patients is described in section 15.

## **8.0 PRETREATMENT EVALUATION**

Prior to initiating treatment:

- Histopathologic confirmation of HL; if unconfirmed, patients will be required to undergo biopsy of most accessible PET-avid lesion. For patients who have undergone biopsy confirmation of relapse following their most recent therapy, tissue blocks and unstained slides will be obtained for confirmation and correlative studies.

Within 4 weeks prior to initiating treatment:

- Medical history and demographics
- Complete history and physical exam (including weight, pulse, blood pressure, temperature, ECOG performance status)
- Medication review
- Blood work: CBC with differential, PT/INR, aPTT, electrolytes (Na, K, Cl, CO<sub>2</sub>), BUN, Cr, total bilirubin, total protein, albumin, AST, ALT, alkaline phosphatase, magnesium, phosphorus, LDH, amylase, lipase
- Thyroid function testing (TSH, free T<sub>3</sub>, and free T<sub>4</sub>)
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)
- Hepatitis B surface antigen and Hepatitis B core antibody
- Hepatitis C antibody
- Serum beta-HCG (for WOCBP only) to assess for pregnancy
- PET scan
- Separate CT chest/abdomen/pelvis and neck CT if clinically indicated (MRI will be used for those who are unable to undergo CT scans)

## **9.0 TREATMENT/INTERVENTION PLAN**

The dose level of Atezolizumab to be tested in this study is 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) administered by IV infusion, beginning on C1D1 and on D1 of each 3-week treatment cycle after all procedures and assessments have been completed. Atezolizumab will be delivered in infusion bags with IV infusion lines that have product contacting surfaces of polyvinyl chloride (PVC) or polyolefin and 0.2 µm in-line filters (filter membrane of polyethersulfone [PES]). Administration of Atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. The initial dose of Atezolizumab will be delivered over 60 (± 15) minutes. If the first infusion is tolerated

without infusion-associated AEs, the second infusion may be delivered over 30 ( $\pm$  10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 ( $\pm$  10) minutes. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [ $\pm$  5] minutes), and 30 ( $\pm$  10) minutes after the infusion. For all subsequent infusions, vital signs will be collected within 60 minutes before and within 30 minutes after the infusion, but not during the infusion unless clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

### **9.1 Treatment Schema**

All patients will receive atezolizumab 1200 mg via IV infusion on D1 of each 21-day cycle.

### **9.2 Treatment duration**

Atezolizumab treatment will be given as long as the patient continues to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, any of the other reasons for treatment discontinuation listed in Section 7.1, or a maximum treatment duration of 24 months.

After discontinuation of treatment, patients will complete an EOT visit within 7 days after the last study drug dose and Safety Follow-up visits within 30 days for those patients who have study drug related adverse events at the EOT visit. Patients who have not experienced PD are to be followed every 4 months until PD or they start alternate therapy for their lymphoma.

### **9.3 Dose Adjustments**

There will be no dose reduction for Atezolizumab in this study. Patients may temporarily suspend study treatment for up to 84 days beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced. If Atezolizumab is held because of AEs for > 84 days beyond the scheduled date of infusion, the patient will be discontinued from ATEZOLIZUMAB and will be followed for safety and efficacy.

If a patient must be tapered off steroids used to treat AEs, Atezolizumab may be held for additional time beyond 84 days from the scheduled dose until steroids are discontinued or

reduced to a prednisone dose (or dose equivalent) of  $\leq 10$  mg/day. The acceptable length of interruption will be at the discretion of the investigator.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of principal investigator

#### **9.4 Contraception**

Atezolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if atezolizumab has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

- Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women  $< 45$  years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.).

OR

- Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

- Has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

- Practice abstinence<sup>†</sup> from heterosexual activity;

OR

- Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are<sup>‡</sup>:

Single method (one of the following is acceptable):

- Intrauterine device (IUD)
- Vasectomy of a female subject's male partner
- Contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Cervical cap with spermicide (nulliparous women only)
- Contraceptive sponge (nulliparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication might involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

## **9.5 Use in Pregnancy**

If a subject inadvertently becomes pregnant while on treatment with atezolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Genentech without delay within 2 working days to Genentech if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Genentech. If a



male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Genentech.

## 9.6 Use in Nursing Women

It is unknown whether atezolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

## 10.0 EVALUATION DURING TREATMENT/INTERVENTION

Evaluations during this period are per Table 7.

	Screening		C1D1	C2D1 and D1 of additional cycles	EOT	30 day FU after last dose
Day	-28	-14		+/-3 days	within 7 days following drug discontinuation	+/- 7 days
Obtain Informed Consent	X					
Demography	X					
Inclusion/exclusion criteria	X					
Medical History/ Diagnosis/ Treatment history	X					
Prior/concomitant medications	X		X	X		X
Physical examination	X		X	X	X	X
ECOG and Vitals (Weight, Blood pressure, Pulse, Resp, Temp)	X		X	X	X	
Hematology: CBC with Diff		X	X	X	X	
Chemistry (BMP, TBili, AST, ALT, TP, Alb, AP, LDH, Mag, Phos, amylase, lipase)		X	X	X	X	
Serum Cytokines			X	X	X	
Coagulation (aPTT and PT/INR)		X				
Urinalysis		X	X	X	X	
Serum/Urine beta-HCG for women of childbearing age	X			As clinically indicated		
Hepatitis B/C	X			As clinically indicated		
Thyroid function testing (TSH, free T3, and free T4)	X			As clinically indicated		

Radiographic assessment	X			After every 3 cycles until C12, and then every 4 cycles thereafter	X (if not done within 4 weeks)	
Fresh Tumor biopsy	X*			X	X	
Research blood tests			X	X (C2D1 only)	X	

\*Pre-treatment fresh tumor biopsy for patients without pathologic confirmation of relapsed disease prior to study enrollment.

Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly.

### 10.1 Laboratory Assessments

Laboratory assessments will include the following:

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Serum chemistries (glucose, BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin)
- Coagulation (aPTT and INR)
- Pregnancy test (for women of childbearing potential)
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)
- Serum cytokine panel (IL-10, IL-6, IL-1B, TNF-α)
- Thyroid function testing (TSH, free T3, and free T4), Epstein-Barr virus (EBV) serology (EBNA IgG), hepatitis B virus (HBV) serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen), and HCV serology (anti-HCV) as clinically indicated
  - HBV DNA test is required for patients who have known positive serology for anti-HBc
  - HCV RNA test is required for patients who have known positive serology for anti-HCV

- All patients will undergo a tumor biopsy sample collection, if clinically feasible, at the first evidence of early radiographic disease progression (i.e., not preceded by meaningful tumor regression). Acceptable samples include core needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

## **10.2 Physical Examination**

A complete physical examination will be performed at screening and at the treatment discontinuation visit and should include the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems.

A limited physical examination will be performed at other visits to assess changes from baseline abnormalities and any new abnormalities and to evaluate patient-reported symptoms. New or worsened abnormalities should be recorded as AEs if appropriate.

As part of tumor assessments, a physical examination should also include the evaluation of the presence and degree of enlarged lymph nodes, skin neoplasm, hepatomegaly, and splenomegaly.

## **10.3 Medical History**

Medical history includes clinically significant diseases within the previous 5 years, smoking history, cancer history (including tumor characteristics such as hormone receptor status), prior cancer therapies and procedures, and all medications used by the patient within 7 days before the screening visit (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies).

## **10.4 Vital Signs**

Vital signs will include measurements of heart rate, respiratory rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature.

For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [ $\pm$  5] minutes), and 30 ( $\pm$  10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before and within 30 minutes after the infusion. Vital signs should be collected during the infusion only if clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

## **10.5 Correlative Studies**

### **Rationale for correlative studies**

We hypothesize that PD-L1 blockade with atezolizumab will promote sustained responses in Hodgkin lymphomas by promoting clonal T cell responses, and b) inhibiting pro-survival back-signaling through PD-L1. We propose a series of correlative analyses that will characterize changes in tumor-infiltrating T-cells and HL RS cells in response to treatment. These will include assays performed on both primary tumor tissue obtained both prior to and on treatment and on peripheral blood obtained throughout the course of therapy:

### **Acquisition of biospecimens**

#### Biopsies

All patients without pathologic confirmation of relapsed or refractory HL will undergo IR-guided core biopsy prior to initiation of treatment with Atezolizumab (denoted “pre-treatment biopsy” below). All patients undergo repeat IR-guided core biopsy when technically feasible, and fine needle aspiration when core biopsy is deemed to be technically difficult, before cycle 2 of therapy (denoted “on-treatment biopsy” below). When technically feasible, a total of eight to ten (8-10) cores will be obtained with each biopsy for morphologic review and correlative studies (described below). Biopsies will be placed in RPMI-1640 media and sent either directly to the pathology department for flow cytometry and sorting (described below) or viably cryopreserved at -80°C in 90% fetalbovine serum (FBS) and 10% DMSO until needed.

#### Peripheral blood

All patients will have 5 additional tubes of blood drawn on C1D1, C2D1, and at the end of treatment. Serum will be frozen and peripheral blood mononuclear cells will be viably cryopreserved from all tubes.

#### Proposed assays

1. Immunohistochemistry of pre-treatment patient biopsies: Three (3) pre-treatment and on-treatment core biopsies will be fixed in formaldehyde and allocated for morphologic review and immunohistochemistry (IHC). Immunohistochemical staining will be performed with antibodies against MHC-I, MHC-II, PD-1, PD-L1, PD-L2, FoxP3, FasL, TRAIL, phospho-S6 (S235/236), and phosphor-Akt (S473). We will follow previously well-established protocols for IHC analysis of FFPE tissue (Vose et al JCO 2008, Iqbal et al Blood 2014).
2. Flow cytometry analysis and sorting of pre and on-treatment patient biopsies: Five (5) pre-treatment and on-treatment core biopsies will be placed in RPMI media and sent to the pathology department, where single cell suspensions will be generated. Clinical flow cytometry using 3-laser BD-FACSCANTO-10 instrument (Becton Dickinson Immunocytometry Systems (BDIS)) and 9-10 color assays will be

performed with specific emphasis on markers likely to be affected by treatment with pembrolizumab, including:

Basic T-cell subsets: CD3<sup>+</sup> T cells and 2 subsets: CD3<sup>+</sup>CD4<sup>+</sup> and CD3<sup>+</sup>CD8<sup>+</sup>.

Effector and memory subsets: defined by CD45RA, CD28, CD27, and CCR7

Regulatory T cells: defined by CD4, CD25, CD127, and CCR4.

Activation/exhaustion: defined by expression of PD-1, LAG-3, TIM-3, and CTLA-4

3. TCR clonality evaluation: Flow-cytometry-sorted CD4<sup>+</sup> and CD8<sup>+</sup> T cells from both pre and on-treatment biopsies and peripheral blood mononuclear cells will be separated and DNA will be promptly extracted using a low-input DNA extraction kit (Promega). Clonal TCR diversity will be assessed using the Adaptive ImmunoSEQ kit. The resulting multiplexed PCR product will be sequenced on an Illumina MiSeq system and analyzed using the ImmunoSEQ analyzer.
4. RNA-sequencing of HLRS cells: Flow-cytometry-sorted RS cells will undergo low-input RNA extraction, cDNA synthesis, and RNA sequencing as previously described (Reichel et al Blood 2015).
5. Multiplexed serum cytokine analysis: Sera or plasma from patients will be collected at C1D1, C2D1, and at the end of and stored at -20°C. Circulating levels of six cytokines (IFN- $\gamma$ , TNF- $\alpha$ , IL-2, IL-4, IL-5 or IL-10) and chemokines (CXCL8/IL-8, CCL5/RANTES, CXCL9/MIG, CCL2/MCP-1, and CXCL10/IP-10) will be assessed via a cytometric bead array kit from BD biosciences as per the manufacturer's instruction. Briefly, bead populations with distinct fluorescence intensities are coated with capture antibodies specific for the above cytokines and chemokines. Two-color cytometric analysis will be carried out using flow cytometry. Data will be obtained and analyzed by CBA software. Data are analyzed in dot-plot FL-2 vs. FL-3; the six FL-3 particles with different fluorescent intensities are distributed along the axis. A single set of diluted standards is used to generate a standard curve for each analyte (standard ranging from 0 to 5000 pg/ml). The concentration of the cytokine calibrators is expressed vs. median fluorescence intensity (FL-2) (MFI) in the standard curves.

**Clinical Correlation**: Data obtained above will be correlated to clinical outcomes including best response and progression-free survival, to determine whether any of the correlative data serves as a predictive or prognostic biomarker for patients treated with atezolizumab.

The above studies may provide biologically relevant parameters, both for determining patients who are more likely to respond to therapy as well as to monitor correlates of antitumor immunity, particularly in the peripheral blood, where they may serve as a useful monitoring tool. Correlative studies of patients treated with checkpoint inhibitors

have demonstrated evidence of on-target efficacy in peripheral blood mononuclear cells, but whether this correlates with duration or efficacy of therapy is unknown. Understanding the biology of the tumor microenvironment both pre-/post-treatment will be critical for evaluating the role that these immunomodulatory drugs play in inducing an effective antitumor immune response. Examination of biopsies both pre- and post treatment will be critical to exploring this area, as this is thought to be the primary site where restoration of antitumor immune responses occurs. Thus, evaluation of the tumor microenvironment via the approaches described above will be critical to determine the mechanism by which antitumor immunity is restored in response to therapy and to develop rational biomarkers for selecting appropriate patients and monitoring responses on treatment.

#### **Prioritization of correlative studies**

The correlative plan above designates allocation of ten (10) cores from pre-treatment and on-treatment biopsies. Should fewer samples be obtained, the priority for allocation of core biopsy samples will be as follows:

<b>Core</b>	<b>Allocation</b>
1	FFPE for IHC
2	Flow cytometry and sorting
3	Flow cytometry and sorting
4	FFPE for IHC
5	Flow cytometry and sorting
6	Snap frozen
7	FFPE for IHC
8	Flow cytometry and sorting
9	Snap frozen
10	FFPE for IHC

#### **Treatment Discontinuation Visit**

Patients who discontinue from treatment will be asked to return to the clinic no more than 30 days after the last treatment for a treatment discontinuation visit. The visit at which a response assessment shows progressive disease may be used as the treatment discontinuation visit.

## **11.0 TOXICITIES/SIDE EFFECTS**

### **11.1 General Plan to Manage Safety Concerns.**

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria (see Section 6.1 and Section 6.2) and close monitoring (as indicated below). See Section 16.2 for complete details regarding safety reporting for this study.

#### **Eligibility Criteria**

Eligibility criteria were selected to guard the safety of patients in this trial. Results from the nonclinical toxicology studies with Atezolizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were taken into account (see Section 5.2).

#### **Monitoring**

Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, defined and graded according to NCI CTCAE v4.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Section 10. Patients will be followed for safety for 30 days following the last dose of study treatment or until receipt of another anticancer therapy, whichever comes first.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Section 9 and 10 for the list and timing of study assessments). All serious adverse events (SAEs) and protocol-defined events of special interest (see Section 17.2) will be reported in an expedited fashion. In addition, the investigators will review and evaluate observed AEs on a regular basis.

Patients who have an ongoing study treatment-related AE upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anticancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.

### **11.2 Guidelines for Dosage Modification and Treatment Interruption or Discontinuation**

Atezolizumab treatment will be given as long as the patient continues to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, any of the other reasons for treatment discontinuation listed in Section 7.1, or a maximum treatment duration of 24 months.

There will be no dose reduction for Atezolizumab in this study. Patients may temporarily suspend study treatment for up to 84 days beyond the scheduled date of delayed infusion

if study drug-related toxicity requiring dose suspension is experienced. If Atezolizumab is held because of AEs for > 84 days beyond the scheduled date of infusion, the patient will be discontinued from ATEZOLIZUMAB and will be followed for safety and efficacy as specified in Section 17.2.

If a patient must be tapered off steroids used to treat AEs, Atezolizumab may be held for additional time beyond 84 days from the scheduled dose until steroids are discontinued or reduced to a prednisone dose (or dose equivalent) of  $\leq 10$  mg/day. The acceptable length of interruption will be at the discretion of the investigator.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of investigator.

Any toxicity associated or possibly associated with Atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology. Although most AEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of Atezolizumab may not have an immediate therapeutic effect, and there is no available antidote for Atezolizumab. In severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNF $\alpha$  inhibitors.

Patients should be assessed clinically (including review of laboratory values) for toxicity prior to, during, and after each infusion. If unmanageable toxicity due to Atezolizumab occurs at any time during the study, treatment with Atezolizumab should be discontinued.

Management of hepatitis/transaminitis, colitis, rash, and hypothyroidism are presented in this section as they have been observed with Atezolizumab and are potentially immune related.

### **Gastrointestinal Toxicity**

Immune-mediated colitis has been associated with the administration of Atezolizumab. Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild.

If the event is of significant duration or magnitude, or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP or platelet count or bandemia), it is recommended that sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy with three to five specimens for standard paraffin block be performed. If possible, one or two biopsy specimens should be snap frozen and stored.

Treatment may be restarted following the resolution of colitis. In addition, if the patient is being managed with corticosteroids, treatment should not be restarted until the steroids



have been tapered down to a prednisone dose  $\leq 10$  mg/day. Patients who resume treatment should be monitored closely for signs of renewed diarrhea. Table 1 provides a summary of dose modification guidelines for gastrointestinal toxicities.

**Table 1 Dose Modification Guidelines for Gastrointestinal Toxicity**

Toxicity	Description	Management
Diarrhea	Grade 2 (4–6 stools per day over baseline) < 5 days	Hold Atezolizumab and discontinue NSAIDS (or other medications known to exacerbate colitis). Investigate for etiology. Restart Atezolizumab once at baseline stool frequency.
	Grade 2 (4–6 stools per day over baseline) > 5 days	Hold ATEZOLIZUMAB and discontinue NSAIDS (or other medications known to exacerbate colitis) while etiology is being investigated. Consider referral to a gastroenterologist. Administer anti-diarrheal agent (e.g., Imodium®). Consider oral budesonide, mesalamine, or 10 mg oral prednisone equivalent per day. Restart Atezolizumab once at baseline stool frequency.
	Abdominal pain	Hold ATEZOLIZUMAB and discontinue NSAIDS (or other medications known to exacerbate colitis).
	Blood or mucus in stool	Rule out bowel perforation. Consider administering prednisone 60 mg/day or equivalent.
	OR	Taper steroids over 1 month. Restart ATEZOLIZUMAB if diarrhea is resolved and systemic steroid dose is ≤ 10 mg oral prednisone equivalent per day.
	Grade ≥ 3 (≥ 7 stools/day over baseline) with peritoneal signs, ileus, or fever	Permanently discontinue Atezolizumab for life-threatening, immune-related diarrhea or colitis.

NSAD = nonsteroidal anti-inflammatory drug.

## Hepatotoxicity

Immune-mediated hepatitis has been associated with the administration of Atezolizumab.

While in this study, patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately, and LFTs should be reviewed before administration of the next dose of study drug.

If LFTs increase, neoplastic, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes of increased LFTs. Anti-nuclear antibody, peri-nuclear anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal, and anti-smooth muscle antibody tests should be performed if an autoimmune etiology is considered.

Patients with LFT abnormalities should be managed according to the guidelines in Table 2.

**Table 2 Dose Modification Guidelines for Hepatotoxicity**

Toxicity	Description	Management
LFT abnormalities	AST/ALT ( $> \text{ULN}$ to $3 \times \text{ULN}$ ) with total bilirubin $< 2 \times \text{ULN}$	Continue with the standard monitoring plan (i.e., LFTs every 3 weeks before dosing).
	AST/ALT ( $> 3 \times \text{ULN}$ to $< 10 \times \text{ULN}$ ) with total bilirubin $< 2 \times \text{ULN}$	Continue Atezolizumab. Monitor LFTs at least weekly. Consider referral to a hepatologist.
	AST/ALT $> 10 \times \text{ULN}$	Hold Atezolizumab. Consider administering IV steroids for 24–48 hours (prednisone 60 mg/day equivalent) followed by an oral prednisone (or equivalent) taper over 2–4 weeks. If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or $\text{TNF}\alpha$ antagonist) to the corticosteroid regimen may be considered. Monitor LFTs every 48–72 hours until decreasing and then follow weekly. Restart Atezolizumab if AST/ALT $\leq 3 \times \text{ULN}$ with bilirubin $< 2 \times \text{ULN}$ and steroid dose is $\leq 10$ mg oral prednisone equivalent per day. Permanently discontinue Atezolizumab for life-threatening, immune-related hepatic events.

**Table 2 Dose Modification Guidelines for Hepatotoxicity (cont.)**

Toxicity	Description	Management
LFT abnormalities (cont.)	AST/ALT $\geq 3 \times$ ULN with bilirubin $> 2 \times$ ULN	Hold Atezolizumab. Consult a hepatologist. Consider administering IV steroids for 24–48 hours (prednisone 60 mg/day equivalent) followed by oral taper over 1 month. If LFTs results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNF $\alpha$ antagonist) to the corticosteroid regimen may be considered. Monitor LFTs every 48–72 hours until decreasing and then follow weekly. Restart Atezolizumab if AST/ALT $\leq 3 \times$ ULN with bilirubin $< 2 \times$ ULN and steroid dose is $\leq 10$ mg oral prednisone equivalent per day.

IV = intravenous; LFT = liver function test; TNF $\alpha$  = tumor necrosis factor alpha; ULN = upper limit of normal.

### **Dermatologic Toxicity**

Treatment-emergent rash has been associated with Atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus.

A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be performed unless contraindicated. Low-grade rash and pruritus AEs have been treated with symptomatic therapy (e.g., antihistamines). Topical or parenteral corticosteroids may be required for more severe symptoms.

Dermatologic toxicity and rash should be managed according to the guidelines in Table 3.

**Table 3 Dose Modification Guidelines for Dermatologic Toxicity**

Toxicity	Description	Management
Dermatologic toxicity/rash (e.g., maculopapular or purpura)	Grade 1: Mild < 10% BSA	Continue ATEZOLIZUMAB symptomatic therapy with antihistamine PRN. Consider topical steroids and/or other symptomatic therapy (e.g., antihistamines).
	Grade 2: Moderate 10%–30% BSA	Continue ATEZOLIZUMAB. Consider dermatologist referral. Administer topical steroids. Consider higher potency topical steroid if rash is unresolved.
	Grade 3: Severe > 30% BSA	Hold ATEZOLIZUMAB. Consult dermatologist. Administer oral prednisone 10 mg or equivalent. If the rash is unresolved after 48–72 hours, administer oral prednisone 60 mg or equivalent. Restart ATEZOLIZUMAB if rash is resolved and systemic dose is $\leq 10$ mg oral prednisone equivalent per day. Permanently discontinue ATEZOLIZUMAB for life-threatening, immune-related dermatologic toxicity.

BSA = body surface area; PRN = as needed.

### Endocrine Toxicity

Hypothyroidism has been associated with the administration of ATEZOLIZUMAB.

Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies, as well as for hyponatremia or hyperkalemia. An endocrinologist should be consulted if an endocrinopathy is suspected.

Thyroid-stimulating hormone (TSH) and free T4 levels should be obtained to determine whether thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

Hypothyroidism should be managed according to the guidelines in Table 4.

**Table 4 Dose Modification Guidelines for Endocrine Toxicity**

Toxicity	Description	Management
Hypothyroidism	TSH elevated, asymptomatic	Continue ATEZOLIZUMAB. Start thyroid-replacement hormone. Monitor TSH weekly.
	TSH elevated, symptomatic	Hold ATEZOLIZUMAB. Consider referral to an endocrinologist. Restart ATEZOLIZUMAB when symptoms are controlled by thyroid replacement and TSH levels are decreasing.

TSH = thyroid-stimulating hormone.

### **Pulmonary Toxicity**

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of ATEZOLIZUMAB and have primarily been observed in patients with underlying NSCLC.

Mild-to-moderate events of pneumonitis have been reported with ATEZOLIZUMAB. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease (COPD), or pulmonary hypertension and the following should be performed:

- Measurement of oxygen saturation (i.e., arterial blood gas)
- High-resolution CT scan of the chest
- Bronchoscopy with bronchoalveolar lavage and biopsy
- Pulmonary function tests (with diffusion capacity of the lung for carbon monoxide [DL<sub>CO</sub>])

Patients will be assessed for pulmonary signs and symptoms throughout the study. Patients will also have CT scans of the chest at every tumor assessment.

Pulmonary toxicity should be managed according to the guidelines in Table 5.

**Table 5 Dose Modification Guidelines for Pulmonary Toxicity**

Toxicity	Description	Management
Pulmonary toxicity	GGO or non-infectious infiltrate in absence of hypoxia, or dyspnea	Hold treatment with ATEZOLIZUMAB. Re-evaluate after 1 week. If no worsening in GGO/infiltrates and patient still asymptomatic, resume treatment with ATEZOLIZUMAB. If GGO/infiltrates worsen and patient is still asymptomatic, continue to hold ATEZOLIZUMAB and refer for bronchoscopy. Consider starting low-dose oral prednisone 10 mg or equivalent. Re-evaluate after 1 week. Resume ATEZOLIZUMAB if GGO/infiltrates improving.
	Hypoxia or dyspnea in presence of GGO or infiltrate without alternative etiology	Hold ATEZOLIZUMAB. Consult a pulmonologist. Investigate for other etiologies and consider bronchoscopy. If bronchoscopy is consistent with immune-related etiology, start 60 mg prednisone equivalent per day followed by taper over 2 weeks. Restart ATEZOLIZUMAB if symptomatically improved, infiltrates are resolved, and steroid use is $\leq$ 10 mg prednisone equivalent per day. Permanently discontinue ATEZOLIZUMAB for life-threatening, immune-related pulmonary events.

GGO = ground glass opacities.

#### **Potential Pancreatic Toxicity**

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with administration of other immunomodulatory agents. The differential diagnosis of acute abdominal pain should

include pancreatitis. Appropriate workup should include an evaluation for obstruction, as well as serum amylase and lipase tests.

### **Potential Eye Toxicity**

An ophthalmologist should evaluate visual complaints. Uveitis or episcleritis may be treated with topical corticosteroid eye drops. ATEZOLIZUMAB should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

Ocular toxicity should be managed according to the guidelines in Table 6.

**Table 6 Dose Modification Guidelines for Eye Toxicity**

Toxicity	Description	Management
Eye toxicity (autoimmune uveitis, iritis, or episcleritis)	Symptomatic	Hold ATEZOLIZUMAB. Consult ophthalmologist and start topical corticosteroid eye drops. ATEZOLIZUMAB may be restarted following resolution of the events. Permanently discontinue ATEZOLIZUMAB for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

## **12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT**

### **12.1 Tumor and Response Evaluation**

Response and progression of disease will be evaluated in this study using the RECIL criteria<sup>23</sup>. Clinical evaluation and tumor assessments will be performed periodically, as is indicated in Table 7, based on physical examination, radiological evaluation and core bone marrow biopsy (in patients with pre-existing bone marrow involvement). Clinical suspicion of disease progression at any time will require a physical examination and radiological confirmation to be performed promptly, rather than waiting for the next scheduled tumor assessment. In case of an unscheduled or delayed tumor assessment for any reason, subsequent tumor assessments must be performed according to the originally planned schedule from baseline. Patients who withdraw due to toxicity will be considered study failures at the time of withdrawal; patients withdrawing before first response assessment will be considered primary treatment failures.



## **Measurability of lesion for objective response**

- Measurable disease: lesions that can be accurately measured in two dimensions by CT, MRI, plain x-ray or other conventional technique and have a greatest transverse diameter of 1.5 cm or greater.
- Non-measurable disease: All other lesions including uni dimensional lesions, lesions too small to be considered measurable, pleural or pericardial effusions, ascites, bone disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed by CT, or disease documented only by indirect evidence (e.g. lab values).
- Patients may receive palliative radiotherapy to an isolated site of disease progression so long as they are deemed by their treating physician to be continuing to derive clinical benefit from ATEZOLIZUMAB. However, for purposes of response assessment this will be considered progression of disease.

Assessment of tumor burden in lymphoma clinical trials can use the sum of longest diameters (SLD). In patients with disseminated disease, a maximum of three target lesions should be selected and used to estimate tumor response. Target lesions should be selected from those with the largest size that can be reproducibly measured and preferably representing multiple sites and/organs. In most cases, lymph nodes can be considered target lesions if the lymph node longest diameter measures  $\geq 15$  mm. Similar to RECIST 1.1, a lymph node measuring between 10 and 14 mm is considered abnormal but should not be selected as a target lesion. Lymph nodes measuring  $< 10$  mm in diameter are considered normal. In certain anatomical sites (inguinal, axillary, and portocaval), normal lymph nodes may exist in a narrow, elongated form, and such nodes should not be selected as target lesions if alternatives are available. Extranodal lesions are selected as target lesions if they have soft tissue component, based on their size, and the ease of reproducibility of repeated measurements, with a minimum measurement of the longest diameter of  $\geq 15$  mm. All other lesions should be identified as nontarget lesions and should be recorded at baseline, without the need to measure them. Nontarget lesions should be followed and reported as present, absent, or clear progression.

## **Objective disease response assessment**

Objective status is to be recorded at each evaluation according to the RECIL Criteria [31].

## **EVALUATION, STAGING, AND RESPONSE ASSESSMENT FOR HODGKIN AND NON-HODGKIN LYMPHOMA: THE RECIL CRITERIA [31]**

**Table 7. RECIL 2017: Criteria for RECIL Response Assessment of Lymphoma**

% Change in sum of diameters of target lesions from nadir					
	CR	PR	MR <sup>a</sup>	SD	PD
% change from baseline	<ul style="list-style-type: none"> <li>Complete disappearance of all target lesions and all nodes with long axis &lt;10mm.</li> <li>≥30% decrease in the sum of longest diameters of target lesions (PR) with normalization of FDG-PET</li> </ul>	≥30% decrease in the sum of longest diameters of target lesions but not a CR	≥10% decrease in the sum of longest diameters of target lesions but not a PR (<30%)	<10% decrease or ≤ 20% increase in the sum of longest diameters of target lesions	<ul style="list-style-type: none"> <li>&gt;20% increase in the sum of longest diameters of target lesions</li> <li>For small lymph nodes measuring &lt;15 mm post therapy, a minimum absolute increase of 5 mm and the long diameter should exceed 15 mm</li> <li>Appearance of a new lesion</li> </ul>
FDG-PET	Normalization of FDG-PET (Deauville score 1-3)	Positive (Deauville score 4-5)	Any	Any	Any
Bone marrow involvement	Not involved	Any	Any	Any	Any
New lesions	No	No	No	No	Yes or No

CR, complete response; CT, computerized tomography; FDG-PET, [<sup>18</sup>F]2-fluoro-2-deoxy-D-glucose; MR, minor response; PD, progression of disease; PR, partial response; SD, stable disease.  
<sup>a</sup>A provisional category.

### **13.0 CRITERIA FOR REMOVAL FROM STUDY**

#### **13.1 Patient Discontinuation**

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Disease progression
- Ineligibility (at the pretreatment evaluation) of the patient as defined in the inclusion/ exclusion criteria
- Treatment will be discontinued at the request of the patient, refusal of therapy, non-compliance, or upon the development of an intercurrent significant medical illness.
- Significant protocol violation
- Unacceptable toxicity
- Decision by the investigator that termination is in the patient's best medical interest.
- Loss to follow-up
- Development of active HBV infection, hepatitis, or HIV infection
- Pregnancy or a positive pregnancy test
- Death of the patient

In addition to the general study treatment withdrawal criteria, the following study specific criteria will also require premature study treatment discontinuation:

- Use of prohibited medication
- Start of any other anti-neoplastic therapy

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate Case Report Form (CRF). However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will **not** be replaced and they will be considered study failures at that point. Patients who withdraw prior to first response assessment will be considered treatment failures.

See Section 8 for assessments that are to be performed for patients who prematurely withdraw from the study during the treatment period.

### **14.0 BIostatistics**

This is a phase II study in which we are aiming to evaluate for evidence of activity of anti-PD-L1 therapy in rel/ref HL. The primary endpoint for both cohorts is 12 month progression-free survival (PFS). For patients previously treated with anti-PD-1 therapy, based on historical data showing a 12-month PFS of 9% [Vardhana, unpublished], a 12m PFS rate of 10% is considered undesirable and 30% considered desirable. With a Simon two-stage minimax design with type-I error of 0.05 and power of 0.8, 15 patients will be enrolled at the first stage. If less than 2 patients are alive and progression-free by 12 months, the trial will stop and the therapy will be considered not efficacious. If  $\geq 2$  patients are alive and progression-free by 12 months, then additional 10 patients will be enrolled in the second stage to make the total sample size 25. If less than 6 of the 25 patients are alive and progression-free by 12 months, the therapy will be considered not promising. If  $\geq 6$  of the 25 patients are alive and progression-free by 12 months, the therapy will be considered promising for the anti-PD-1 refractory patients.

For patients never treated with anti-PD-1 therapy before, based on historical data showing a median PFS of 10 months and a 12-month PFS of 46% [116, 117], a 12m PFS rate of 40% is considered undesirable and 62% considered desirable. With a Simon two-stage minimax design with type-I error of 0.05 and power of 0.8, 20 patients will be enrolled at the first stage. If less than 9 patients are alive and progression-free by 12 months, the trial will stop and the therapy will be considered not efficacious. If  $\geq 9$  patients are alive and progression-free by 12 months, then additional 12 patients will be enrolled in the second stage to make the total sample size 32. If less than 18 of the 32 patients are alive and progression-free by 12 months, the therapy will be considered not promising. If  $\geq 18$  of the 32 patients are alive and progression-free by 12 months, the therapy will be considered promising for the anti-PD-1 native patients.

As mentioned in Section 4.1, we will first open cohort 1 with patients previously treated with anti-PD-1 therapy. Should cohort 1 not meet criteria for early stopping at the end of the first stage, we will open a second cohort which will include patients who never received anti-PD-1 therapy.

In both cohorts, the recruitment will continue at the end of the first stage without halting. There is a probability that more patients than necessary will be enrolled when the therapy is not efficacious. However, if there are an excess of early progressions, the first stage stopping rule will catch them. Moreover, the two-stage design is nevertheless better than a single stage design, which requires the same sample size, and efficacy criterion yet recruits the full cohort regardless of the interim outcome.

## **14.1 Outcomes Measures**

### **Primary Efficacy Outcome Measure**

The primary endpoint of this study is 12 month PFS in both cohorts. The primary endpoint will be computed as proportions along with exact 95% confidence intervals. Patients withdrawn from the study for reason of pregnancy will be replaced and not be evaluated for the primary endpoint; however, patients withdrawn for all other reasons will be considered as progression so long as they have received any study treatment.

### **Secondary Efficacy Outcome Measures**

Secondary endpoints include determination of the overall response rate (defined as CR or PR as best overall response), disease control rate (defined as CR or PR as best response or SD for 2 or more assessments), complete response rate, progression free survival, and duration of response (defined for those who respond as time from documented objective response (CR or PR) until progression) of atezolizumab in relapsed/refractory HL patients who are anti-PD-1 previously treated (cohort 1) and in relapsed/refractory HL patients who are treatment naïve (cohort 2). Patients will undergo disease assessment with PET/CT every 3 cycles for the first 12 cycles and subsequently every 4 cycles until treatment intolerance, disease progression, or 2 years of treatment. PFS and duration of response will be computed by Kaplan Meier method.

Exploratory goals are to determine whether pre-treatment tumor expression of MHC-I, MHC-II, PD-L1, or PD-L2, the effector to regulatory T cell ratio at baseline and change in ratio in response to therapy, changes in expression of T-cell extrinsic apoptosis-related markers FasL and TRAIL in response to therapy, or PI3K activation on HRS cells at baseline or change in PI3K activation in response to therapy predicts treatment response in terms of PFS and overall response rate. With the exception of pre-treatment MHC-I and MHC-II, which will be treated as categorical variables, all other correlative measures will be treated as continuous variables. Wilcoxon rank sum tests will be used for correlation between the continuous variables and overall response rate. Fisher's exact will be used for correlation between categorical variables and overall response rate. Cox's proportional hazards model will be used for correlation with PFS. Other measurements from the proposed assays will be summarized by descriptive statistics.

### **Safety Outcome Measures**

Toxicity will be graded using CTCAE (version 4) guidelines and will be compared to toxicity observed with anti-PD-1 in HL.

## **15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES**

## **15.1 Research Participant Registration**

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

## **15.2 Randomization**

No randomization will occur on this study.

## **16.0 DATA MANAGEMENT ISSUES**

This clinical research study will be monitored both internally by the PI and externally by the MSKCC IRB. In terms of internal review, the PI will continuously monitor and tabulate AEs. Appropriate reporting to the MSKCC IRB will be made. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled,
- Stopping rules for toxicity and/or response are met,
- Risk/benefit ratio is not altered to the detriment of the subjects,
- Appropriate internal monitoring of AEs and outcomes is done,
- Over-accrual does not occur,
- Under-accrual is addressed with appropriate amendments or actions, and
- Data are being appropriately collected in a reasonably timely manner.

Routine monitoring will be carried out via a periodic team conference among investigators during which toxicity data, including all SAEs, will be reviewed and other issues relevant to the study such as interim assessment of accrual, outcome, and compliance with study guidelines, will be discussed. Monitoring will be carried out on an ongoing basis. The severity, relatedness, and whether or not the event is expected will be reviewed.

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled in the study, and that data are recorded on the appropriate forms and in a timely manner. Any errors on source data should be lined through, but not obliterated, with the correction inserted, initialed, and dated by the study coordinator or PI. All source documents will be available for inspection by the FDA and the MSKCC IRB.

#### **16.1 Retention of Records**

FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

For studies conducted outside the U.S. under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the FDA IND regulations and the relevant national and local health authorities, whichever is longer.

#### **16.2 Study Medication Accountability**

If study drug will be provided by Genentech, the recipient will acknowledge receipt of the drug by returning the INDRR-1 form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug dispensed from and returned to the study site should be recorded by using the institution's drug inventory log or the National Cancer Institute drug accountability log.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure. Return unopened, expired, or unused study drug with the Inventory of Returned Clinical Material form as directed by Genentech.

### **16.1 Quality Assurance**

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

### **16.2 Data and Safety Monitoring**

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at:

<http://cancertrials.nci.nih.gov/researchers/dsm/index.html>.

The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:

<https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf>

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.



During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

## **17.0 PROTECTION OF HUMAN SUBJECTS**

Potential risks to human subjects include drug related toxicity; pain and discomfort associated with therapy; treatment side effects; phlebotomy; and possible psychologic discomfort from the stresses associated with obtaining imaging studies (e.g., CT scan, PET scan).

If an adverse medical event occurs, the patient will first contact the primary oncologist or the principal investigator. At nights and weekends, there is an oncology physician on call at all times. Patients may either call or come directly to the Urgent Care Center at Memorial Hospital (or to their local emergency room) to be seen.

Costs to the patient (third party insurer) will include the cost of blood tests and diagnostic studies, office visits, and those admissions which may be required as a consequence of treatment-related complications.

All serious adverse events incurred while a patient is on study will be reported to the IRB at Memorial Hospital and Genentech. All serious adverse experiences and relevant laboratory findings will be reported to the principal investigator immediately. An adverse experience is considered serious if death occurs, the condition is life threatening, hospitalization is required, or there is permanent disability or incapacity. All information regarding serious adverse experiences must be recorded on the form provided. Patients suffering serious adverse reactions must be carefully followed and all follow-up information also recorded.

All life threatening and lethal known, unknown, or suspected reactions (toxicities) must be reported to the principal investigator. An SAE report will be submitted to the IRB within 5 days. Any death, regardless of cause, must be reported to the principal investigator by telephone or fax and in writing. It is the treating physician's responsibility to investigate and report the date and cause of death of any patient entered on this trial.

### **17.1 Privacy**

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

## 17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to [saegrade5@mskcc.org](mailto:saegrade5@mskcc.org). All other reports should be sent to [saemskind@mskcc.org](mailto:saemskind@mskcc.org).

For all other trials: Reports that include a Grade 5 SAE should be sent to [saegrade5@mskcc.org](mailto:saegrade5@mskcc.org). All other reports should be sent to [sae@mskcc.org](mailto:sae@mskcc.org).

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

### **Additional SAE reporting Guidelines**

#### Methods and Timing for Assessing and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the U.S. Food and Drug Administration (FDA), appropriate Institutional Review Boards (IRBs), and Genentech, Inc., in accordance with CFR 312.32 (Investigational New Drug [IND] Safety Reports).

#### Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

#### Assessment of Adverse Events

All AEs and SAEs, whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means, will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

**Yes**

There is a plausible temporal relationship between the onset of the AE and administration of ATEZOLIZUMAB, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to ATEZOLIZUMAB; and/or the AE abates or resolves upon discontinuation of ATEZOLIZUMAB or dose reduction and, if applicable, reappears upon re-challenge.

**No**

Evidence exists that the AE has an etiology other than ATEZOLIZUMAB (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to ATEZOLIZUMAB administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected AEs are those AEs that are listed or characterized in the Package Insert (PI) or current Investigator's Brochure.

Unexpected AEs are those not listed in the PI or current Investigator's Brochure or not identified. This includes AEs for which the specificity or severity is not consistent with the description in the PI or Investigator's Brochure. For example, under this definition, hepatic necrosis would be unexpected if the PI or Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis.

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

Diagnosis versus Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is

unknown and cannot be ascertained at the time of reporting, report “Unexplained Death.” Deaths that occur during the protocol-specified adverse event reporting period that are attributed by the investigator solely to progression of disease should be recorded only in the study CRF.

#### Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

#### Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions,
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study, or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

#### Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 90 days after the last dose of study drug. A Pregnancy Report CRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via fax. A pregnancy report will automatically be generated and sent to Genentech Drug Safety. Pregnancy should not be recorded on the Adverse Event CRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event CRF.

A Clinical Trial Pregnancy Reporting Form and fax cover sheet should be completed and faxed to Genentech Drug Safety or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

#### Abortions

Any spontaneous abortion should be classified as an SAE, recorded on the Adverse Event CRF, and reported to Genentech Drug Safety immediately (i.e., no more than 24 hours after learning of the event).

#### Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as an SAE, recorded on the Adverse Event CRF, and reported to Genentech Drug Safety immediately (i.e., no more than 24 hours after learning of the event).

#### Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior ATEZOLIZUMAB exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

#### Safety Reconciliation

The investigator agrees to conduct reconciliation for the product. Genentech and the investigator will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the investigator and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

#### Adverse Events of Special Interest

Adverse events of special interest (AESIs) are defined as a potential safety problem, identified as a result of safety monitoring of the IMP.

The following AEs are considered of special interest and must be reported to the Genentech Drug Safety expeditiously, irrespective of regulatory seriousness criteria:

- Pneumonitis
- Hypoxia or dyspnea, Grade  $\geq 3$
- Endocrinopathies: diabetes mellitus, pancreatitis, or adrenal insufficiency

- Vasculitis
- Hepatitis
- Transaminitis: Grade  $\geq 2$  (AST or ALT  $> 3 \times$  ULN and bilirubin  $> 2 \times$  ULN) or AST/ALT  $> 10 \times$  ULN
- Systemic lupus erythematosus
- Guillain-Barré syndrome
- Myasthenia gravis
- Meningoencephalitis
- Nephritis
- Pericardial effusion
- Skin reactions: vitiligo, pemphigoid
- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome, systemic inflammatory activation, or infusion-reaction syndromes
- Colitis

#### Adverse Event Reporting

Investigators must report all SAEs to Genentech within the timelines described below. The completed MedWatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

**(650) 225-4682**

**OR**

**(650) 225-5288**

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.

SAE reports, whether related or unrelated to ATEZOLIZUMAB, will be transmitted to Genentech within 24 hours of the Awareness Date.

AESIs will be transmitted to Genentech within 15 calendar days of the Awareness Date.

Additional reporting requirements to Genentech include the following:

- Any reports of pregnancy following the start of administration with the ATEZOLIZUMAB and within the follow-up period (for female patients within one year after the last dose of ATEZOLIZUMAB or the partner of a male patient within three months of completing therapy) will be transmitted to Genentech within 24 hours of the Awareness Date.

- All non-serious ATEZOLIZUMAB AEs originating from the study will be forwarded Genentech quarterly.

Note: Investigators should also report events to their IRB as required.

#### MedWatch 3500 A Reporting Guide lines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (item 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the AE to each investigational product and suspect medication

#### Follow-Up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., date of birth, initial, patient number), protocol description and number, if assigned, brief AE description, and notation that additional or follow-up information is being submitted. (The patient identifiers are important so that the new information is added to the correct initial report.)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an AE was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the Medical Science Liaison assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at  
<http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm>

### **17.2.1 Additional Reporting Requirements for IND**



For sponsor IND studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the FDA as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report

The investigator is required to notify the FDA of any fatal or life-threatening AE that is unexpected and assessed by the investigator to be possibly related to the use of ATEZOLIZUMAB. An unexpected AE is one that is not already described in the ATEZOLIZUMAB Investigator's Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of ATEZOLIZUMAB. An unexpected AE is one that is not already described in the ATEZOLIZUMAB Investigator's Brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with analysis of similar events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

**Contact Information for IND Safety Reports**

**FDA fax number for IND safety reports:**

Fax: (800) FDA-0178

**All written IND safety reports submitted to the FDA by the investigator must also be faxed to the following:**

**Genentech Drug Safety Fax:** (650) 225 4682 or (650) 225 5288

**Site's IRB:**

Janelle Walkley

205 East 64th Street, Lower Concourse 173, New York, NY 10065

T 646.449.1338

[walkleyj@mskcc.org](mailto:walkleyj@mskcc.org)

**For questions related to safety reporting, please contact Genentech Drug Safety:**

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-5288

#### IND Annual Reports

Copies of all IND annual reports submitted to the FDA by the investigator should be sent to Genentech Drug Safety via fax:

Fax: (650) 225-4682 or (650) 225-5288

## **18.0 INFORMED CONSENT PROCEDURES**

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

## **19.0 REFERENCES**

1. Canellos, G.P. and D. Niedzwiecki, *Long-term follow-up of Hodgkin's disease trial*. N Engl J Med, 2002. **346**(18): p. 1417-8.

2. Coiffier, B., et al., *CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma*. N Engl J Med, 2002. **346**(4): p. 235-42.
3. Fisher, R.I., et al., *Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma*. N Engl J Med, 1993. **328**(14): p. 1002-6.
4. Federico, M., et al., *R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi*. J Clin Oncol, 2013. **31**(12): p. 1506-13.
5. Cheung, K.J., et al., *Acquired TNFRSF14 mutations in follicular lymphoma are associated with worse prognosis*. Cancer Res, 2010. **70**(22): p. 9166-74.
6. Green, M.R., et al., *Hierarchy in somatic mutations arising during genomic evolution and progression of follicular lymphoma*. Blood, 2013. **121**(9): p. 1604-11.
7. Lohr, J.G., et al., *Discovery and prioritization of somatic mutations in diffuse large B-cell lymphoma (DLBCL) by whole-exome sequencing*. Proc Natl Acad Sci U S A, 2012. **109**(10): p. 3879-84.
8. Morin, R.D., et al., *Mutational and structural analysis of diffuse large B-cell lymphoma using whole-genome sequencing*. Blood, 2013. **122**(7): p. 1256-65.
9. Okosun, J., et al., *Integrated genomic analysis identifies recurrent mutations and evolution patterns driving the initiation and progression of follicular lymphoma*. Nat Genet, 2014. **46**(2): p. 176-81.
10. Pasqualucci, L., et al., *Genetics of follicular lymphoma transformation*. Cell Rep, 2014. **6**(1): p. 130-40.
11. Pasqualucci, L., et al., *Analysis of the coding genome of diffuse large B-cell lymphoma*. Nat Genet, 2011. **43**(9): p. 830-7.
12. Chapman, P.B., et al., *Improved survival with vemurafenib in melanoma with BRAF V600E mutation*. N Engl J Med, 2011. **364**(26): p. 2507-16.
13. Druker, B.J., et al., *Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia*. N Engl J Med, 2006. **355**(23): p. 2408-17.
14. Maemondo, M., et al., *Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR*. N Engl J Med, 2010. **362**(25): p. 2380-8.
15. Rosell, R., et al., *Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial*. Lancet Oncol, 2012. **13**(3): p. 239-46.
16. Imai, K., et al., *Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population*. Lancet, 2000. **356**(9244): p. 1795-9.
17. Penn, I. and T.E. Starzl, *Immunosuppression and cancer*. Transplant Proc, 1973. **5**(1): p. 943-7.
18. Huang, P., et al., *Spontaneous nonthymic tumors in SCID mice*. Comp Med, 2011. **61**(3): p. 227-34.

19. Mottok, A., et al., *Genomic Alterations in CIITA Are Frequent in Primary Mediastinal Large B Cell Lymphoma and Are Associated with Diminished MHC Class II Expression*. Cell Rep, 2015. **13**(7): p. 1418-31.
20. Reichel, J., et al., *Flow sorting and exome sequencing reveal the oncogenome of primary Hodgkin and Reed-Sternberg cells*. Blood, 2015. **125**(7): p. 1061-72.
21. Steidl, C., et al., *MHC class II transactivator CIITA is a recurrent gene fusion partner in lymphoid cancers*. Nature, 2011. **471**(7338): p. 377-81.
22. Kamper, P., et al., *Proteomic analysis identifies galectin-1 as a predictive biomarker for relapsed/refractory disease in classical Hodgkin lymphoma*. Blood, 2011. **117**(24): p. 6638-49.
23. Skinnider, B.F. and T.W. Mak, *The role of cytokines in classical Hodgkin lymphoma*. Blood, 2002. **99**(12): p. 4283-97.
24. van den Berg, A., L. Visser, and S. Poppema, *High expression of the CC chemokine TARC in Reed-Sternberg cells. A possible explanation for the characteristic T-cell infiltrate in Hodgkin's lymphoma*. Am J Pathol, 1999. **154**(6): p. 1685-91.
25. Gandhi, M.K., et al., *Expression of LAG-3 by tumor-infiltrating lymphocytes is coincident with the suppression of latent membrane antigen-specific CD8+ T-cell function in Hodgkin lymphoma patients*. Blood, 2006. **108**(7): p. 2280-9.
26. Green, M.R., et al., *Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma*. Blood, 2010. **116**(17): p. 3268-77.
27. Yamamoto, R., et al., *PD-1-PD-1 ligand interaction contributes to immunosuppressive microenvironment of Hodgkin lymphoma*. Blood, 2008. **111**(6): p. 3220-4.
28. Dong, H., et al., *Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion*. Nat Med, 2002. **8**(8): p. 793-800.
29. Chopra, R., et al., *Autologous versus allogeneic bone marrow transplantation for non-Hodgkin's lymphoma: a case-controlled analysis of the European Bone Marrow Transplant Group Registry data*. J Clin Oncol, 1992. **10**(11): p. 1690-5.
30. Jones, R.J., et al., *Evidence of a graft-versus-lymphoma effect associated with allogeneic bone marrow transplantation*. Blood, 1991. **77**(3): p. 649-53.
31. Younes, A., et al., *International Working Group Consensus Response Evaluation Criteria in Lymphoma (RECIL 2017)*. Annals of Oncology, 2017. p. 1-12.
32. Wiernik, P.H., et al., *Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma*. J Clin Oncol, 2008. **26**(30): p. 4952-7.
33. Witzig, T.E., et al., *Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's Lymphoma*. J Clin Oncol, 2009. **27**(32): p. 5404-9.

34. Freeman, G.J., et al., *Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation*. J Exp Med, 2000. **192**(7): p. 1027-34.
35. Nishimura, H. and T. Honjo, *PD-1: an inhibitory immunoreceptor involved in peripheral tolerance*. Trends Immunol, 2001. **22**(5): p. 265-8.
36. Ahmadzadeh, M., et al., *Tumor antigen-specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired*. Blood, 2009. **114**(8): p. 1537-44.
37. Lee, H.E., et al., *Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer*. Br J Cancer, 2008. **99**(10): p. 1704-11.
38. Leffers, N., et al., *Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer*. Cancer Immunol Immunother, 2009. **58**(3): p. 449-59.
39. Nishimura, H., T. Honjo, and N. Minato, *Facilitation of beta selection and modification of positive selection in the thymus of PD-1-deficient mice*. J Exp Med, 2000. **191**(5): p. 891-8.
40. Latchman, Y., et al., *PD-L2 is a second ligand for PD-1 and inhibits T cell activation*. Nat Immunol, 2001. **2**(3): p. 261-8.
41. Chemnitz, J.M., et al., *SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation*. J Immunol, 2004. **173**(2): p. 945-54.
42. Keir, M.E., et al., *PD-1 and its ligands in tolerance and immunity*. Annu Rev Immunol, 2008. **26**: p. 677-704.
43. Sheppard, K.A., et al., *PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta*. FEBS Lett, 2004. **574**(1-3): p. 37-41.
44. Barber, D.L., et al., *Restoring function in exhausted CD8 T cells during chronic viral infection*. Nature, 2006. **439**(7077): p. 682-7.
45. Konishi, J., et al., *B7-H1 expression on non-small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression*. Clin Cancer Res, 2004. **10**(15): p. 5094-100.
46. Ohigashi, Y., et al., *Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer*. Clin Cancer Res, 2005. **11**(8): p. 2947-53.
47. Thompson, R.H., et al., *Costimulatory B7-H1 in renal cell carcinoma patients: Indicator of tumor aggressiveness and potential therapeutic target*. Proc Natl Acad Sci U S A, 2004. **101**(49): p. 17174-9.
48. Chapuy, B., et al., *Targetable genetic features of primary testicular and primary central nervous system lymphomas*. Blood, 2015.
49. Chen, B.J., et al., *PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies*. Clin Cancer Res, 2013. **19**(13): p. 3462-73.
50. Green, M.R., et al., *Constitutive AP-1 activity and EBV infection induce PD-L1 in Hodgkin lymphomas and posttransplant lymphoproliferative*

- disorders: implications for targeted therapy. Clin Cancer Res, 2012. 18(6): p. 1611-8.*
51. Kiyasu, J., et al., *Expression of programmed cell death ligand 1 is associated with poor overall survival in patients with diffuse large B-cell lymphoma. Blood, 2015. 126(19): p. 2193-201.*
  52. Carreras, J., et al., *High numbers of tumor-infiltrating programmed cell death 1-positive regulatory lymphocytes are associated with improved overall survival in follicular lymphoma. J Clin Oncol, 2009. 27(9): p. 1470-6.*
  53. Kinter, A.L., et al., *The common gamma-chain cytokines IL-2, IL-7, IL-15, and IL-21 induce the expression of programmed death-1 and its ligands. J Immunol, 2008. 181(10): p. 6738-46.*
  54. Myklebust, J.H., et al., *High PD-1 expression and suppressed cytokine signaling distinguish T cells infiltrating follicular lymphoma tumors from peripheral T cells. Blood, 2013. 121(8): p. 1367-76.*
  55. Honda, T., et al., *Tuning of antigen sensitivity by T cell receptor-dependent negative feedback controls T cell effector function in inflamed tissues. Immunity, 2014. 40(2): p. 235-47.*
  56. Das, R., et al., *Combination therapy with anti-CTLA-4 and anti-PD-1 leads to distinct immunologic changes in vivo. J Immunol, 2015. 194(3): p. 950-9.*
  57. Wei, F., et al., *Strength of PD-1 signaling differentially affects T-cell effector functions. Proc Natl Acad Sci U S A, 2013. 110(27): p. E2480-9.*
  58. Nishimura, H., et al., *Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. Immunity, 1999. 11(2): p. 141-51.*
  59. Brahmer, J.R., et al., *Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol, 2010. 28(19): p. 3167-75.*
  60. Blank, C., et al., *PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. Cancer Res, 2004. 64(3): p. 1140-5.*
  61. Garon, E.B., et al., *Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med, 2015. 372(21): p. 2018-28.*
  62. Robert, C., et al., *Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med, 2015. 372(26): p. 2521-32.*
  63. Le, D.T., et al., *PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med, 2015. 372(26): p. 2509-20.*
  64. Motzer, R.J., et al., *Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med, 2015. 373(19): p. 1803-13.*
  65. Ansell, S.M., et al., *PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med, 2015. 372(4): p. 311-9.*
  66. Moskowitz, C.H., et al., *PD-1 Blockade with the Monoclonal Antibody Pembrolizumab (MK-3475) in Patients with Classical Hodgkin Lymphoma after Brentuximab Vedotin Failure: Preliminary Results from a Phase 1b Study (KEYNOTE-013). Blood, 2014. 124(21).*

67. Lesokhin, A.M., et al., *Preliminary Results of a Phase I Study of Nivolumab (BMS-936558) in Patients with Relapsed or Refractory Lymphoid Malignancies*. Blood, 2014. **124**(21).
68. Westin, J.R., et al., *Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial*. Lancet Oncol, 2014. **15**(1): p. 69-77.
69. Topalian, S.L., et al., *Safety, activity, and immune correlates of anti-PD-1 antibody in cancer*. N Engl J Med, 2012. **366**(26): p. 2443-54.
70. Haery, L., R.C. Thompson, and T.D. Gilmore, *Histone acetyltransferases and histone deacetylases in B- and T-cell development, physiology and malignancy*. Genes Cancer, 2015. **6**(5-6): p. 184-213.
71. Li, D., et al., *Regulation of Kruppel-like factor 6 tumor suppressor activity by acetylation*. Cancer Res, 2005. **65**(20): p. 9216-25.
72. Elia, A.E., et al., *Quantitative Proteomic Atlas of Ubiquitination and Acetylation in the DNA Damage Response*. Mol Cell, 2015. **59**(5): p. 867-81.
73. Sakaguchi, K., et al., *DNA damage activates p53 through a phosphorylation-acetylation cascade*. Genes Dev, 1998. **12**(18): p. 2831-41.
74. Sharma, G.G., et al., *MOF and histone H4 acetylation at lysine 16 are critical for DNA damage response and double-strand break repair*. Mol Cell Biol, 2010. **30**(14): p. 3582-95.
75. Morin, R.D., et al., *Frequent mutation of histone-modifying genes in non-Hodgkin lymphoma*. Nature, 2011. **476**(7360): p. 298-303.
76. Pasqualucci, L., et al., *Inactivating mutations of acetyltransferase genes in B-cell lymphoma*. Nature, 2011. **471**(7337): p. 189-95.
77. Coiffier, B., et al., *Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy*. J Clin Oncol, 2012. **30**(6): p. 631-6.
78. O'Connor, O.A., et al., *Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results of the Pivotal Phase II BELIEF (CLN-19) Study*. J Clin Oncol, 2015. **33**(23): p. 2492-9.
79. Olsen, E.A., et al., *Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma*. J Clin Oncol, 2007. **25**(21): p. 3109-15.
80. Kirschbaum, M.H., et al., *A phase 2 study of vorinostat for treatment of relapsed or refractory Hodgkin lymphoma: Southwest Oncology Group Study S0517*. Leuk Lymphoma, 2012. **53**(2): p. 259-62.
81. Younes, A., et al., *Mocetinostat for relapsed classical Hodgkin's lymphoma: an open-label, single-arm, phase 2 trial*. Lancet Oncol, 2011. **12**(13): p. 1222-8.
82. Younes, A., et al., *Panobinostat in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem-cell transplantation: results of a phase II study*. J Clin Oncol, 2012. **30**(18): p. 2197-203.
83. Rosato, R.R., J.A. Almenara, and S. Grant, *The histone deacetylase inhibitor MS-275 promotes differentiation or apoptosis in human leukemia*

- cells through a process regulated by generation of reactive oxygen species and induction of p21CIP1/WAF1*. *Cancer Res*, 2003. **63**(13): p. 3637-45.
84. Saito, A., et al., *A synthetic inhibitor of histone deacetylase, MS-27-275, with marked in vivo antitumor activity against human tumors*. *Proc Natl Acad Sci U S A*, 1999. **96**(8): p. 4592-7.
  85. Lucas, D.M., et al., *The histone deacetylase inhibitor MS-275 induces caspase-dependent apoptosis in B-cell chronic lymphocytic leukemia cells*. *Leukemia*, 2004. **18**(7): p. 1207-14.
  86. Jona, A., et al., *The histone deacetylase inhibitor entinostat (SNDX-275) induces apoptosis in Hodgkin lymphoma cells and synergizes with Bcl-2 family inhibitors*. *Exp Hematol*, 2011. **39**(10): p. 1007-1017 e1.
  87. Fandy, T.E., et al., *Early epigenetic changes and DNA damage do not predict clinical response in an overlapping schedule of 5-azacytidine and entinostat in patients with myeloid malignancies*. *Blood*, 2009. **114**(13): p. 2764-73.
  88. Munshi, A., et al., *Histone deacetylase inhibitors radiosensitize human melanoma cells by suppressing DNA repair activity*. *Clin Cancer Res*, 2005. **11**(13): p. 4912-22.
  89. Cycon, K.A., et al., *Histone deacetylase inhibitors activate CIITA and MHC class II antigen expression in diffuse large B-cell lymphoma*. *Immunology*, 2013. **140**(2): p. 259-72.
  90. Heninger, E., T.E. Krueger, and J.M. Lang, *Augmenting antitumor immune responses with epigenetic modifying agents*. *Front Immunol*, 2015. **6**: p. 29.
  91. Vire, B., et al., *Anti-leukemia activity of MS-275 histone deacetylase inhibitor implicates 4-1BBL/4-1BB immunomodulatory functions*. *PLoS One*, 2009. **4**(9): p. e7085.
  92. Buglio, D., et al., *Vorinostat inhibits STAT6-mediated TH2 cytokine and TARC production and induces cell death in Hodgkin lymphoma cell lines*. *Blood*, 2008. **112**(4): p. 1424-33.
  93. Kroesen, M., et al., *HDAC inhibitors and immunotherapy; a double edged sword?* *Oncotarget*, 2014. **5**(16): p. 6558-72.
  94. Lisiero, D.N., et al., *The histone deacetylase inhibitor, LBH589, promotes the systemic cytokine and effector responses of adoptively transferred CD8+ T cells*. *J Immunother Cancer*, 2014. **2**: p. 8.
  95. Oki, Y., et al., *Immune regulatory effects of panobinostat in patients with Hodgkin lymphoma through modulation of serum cytokine levels and T-cell PD1 expression*. *Blood Cancer J*, 2014. **4**: p. e236.
  96. Shen, L., et al., *Class I histone deacetylase inhibitor entinostat suppresses regulatory T cells and enhances immunotherapies in renal and prostate cancer models*. *PLoS One*, 2012. **7**(1): p. e30815.
  97. Steidl, C., et al., *Tumor-associated macrophages and survival in classic Hodgkin's lymphoma*. *N Engl J Med*, 2010. **362**(10): p. 875-85.
  98. Tan, K.L., et al., *Tumor-associated macrophages predict inferior outcomes in classic Hodgkin lymphoma: a correlative study from the E2496 Intergroup trial*. *Blood*, 2012. **120**(16): p. 3280-7.



99. Haffner, I., et al., *Regulation of arginase-1 expression in macrophages by a protein kinase A type I and histone deacetylase dependent pathway*. J Cell Biochem, 2008. **103**(2): p. 520-7.
100. Pesce, J.T., et al., *Arginase-1-expressing macrophages suppress Th2 cytokine-driven inflammation and fibrosis*. PLoS Pathog, 2009. **5**(4): p. e1000371.
101. Kim, K., et al., *Eradication of metastatic mouse cancers resistant to immune checkpoint blockade by suppression of myeloid-derived cells*. Proc Natl Acad Sci U S A, 2014. **111**(32): p. 11774-9.
102. Armeanu, S., et al., *Natural killer cell-mediated lysis of hepatoma cells via specific induction of NKG2D ligands by the histone deacetylase inhibitor sodium valproate*. Cancer Res, 2005. **65**(14): p. 6321-9.
103. Diermayr, S., et al., *NKG2D ligand expression in AML increases in response to HDAC inhibitor valproic acid and contributes to allorecognition by NK-cell lines with single KIR-HLA class I specificities*. Blood, 2008. **111**(3): p. 1428-36.
104. Jaboin, J., et al., *MS-27-275, an inhibitor of histone deacetylase, has marked in vitro and in vivo antitumor activity against pediatric solid tumors*. Cancer Res, 2002. **62**(21): p. 6108-15.
105. Kato, Y., et al., *Synergistic in vivo antitumor effect of the histone deacetylase inhibitor MS-275 in combination with interleukin 2 in a murine model of renal cell carcinoma*. Clin Cancer Res, 2007. **13**(15 Pt 1): p. 4538-46.
106. Gore, L., et al., *A phase I and pharmacokinetic study of the oral histone deacetylase inhibitor, MS-275, in patients with refractory solid tumors and lymphomas*. Clin Cancer Res, 2008. **14**(14): p. 4517-25.
107. Kummar, S., et al., *Phase I trial of MS-275, a histone deacetylase inhibitor, administered weekly in refractory solid tumors and lymphoid malignancies*. Clin Cancer Res, 2007. **13**(18 Pt 1): p. 5411-7.
108. Ryan, Q.C., et al., *Phase I and pharmacokinetic study of MS-275, a histone deacetylase inhibitor, in patients with advanced and refractory solid tumors or lymphoma*. J Clin Oncol, 2005. **23**(17): p. 3912-22.
109. Younes, A., et al., *The HDAC Inhibitor Entinostat (SNDX-275) Induces Clinical Responses in Patients with Relapsed and Refractory Hodgkin's Lymphoma: Results of ENGAGE-501 Multicenter Phase 2 Study*. Blood, 2011. **118**(21): p. 1168-1168.
110. Robins, H.S., et al., *Comprehensive assessment of T-cell receptor beta-chain diversity in alphabeta T cells*. Blood, 2009. **114**(19): p. 4099-107.
111. Robins, H.S., et al., *Overlap and effective size of the human CD8+ T cell receptor repertoire*. Sci Transl Med, 2010. **2**(47): p. 47ra64.
112. Hardy, M.Y., et al., *A flow cytometry based assay for the enumeration of regulatory T cells in whole blood*. J Immunol Methods, 2013. **390**(1-2): p. 121-6.
113. Oliver, K.G., J.R. Kettman, and R.J. Fulton, *Multiplexed analysis of human cytokines by use of the FlowMetrix system*. Clin Chem, 1998. **44**(9): p. 2057-60.

114. Bellmunt J, Petrylak DP, Powles T, et al. Inhibition of PD-L1 by ATEZOLIZUMAB leads to clinical activity in pts with metastatic urothelial bladder cancer (UBC). *Ann Oncol* 2014;25(S uppl 4):iv280–iv304.
115. Di Giacomo AM, Biagioli M, Maio M. The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications. *Semin Oncol* 2010;37:499–507.
116. Armand P, Shipp MA, Ribrag V et al. Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentixumab vedotin failure. *J Clin Oncol* 2016.
117. Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicenter, multicohort, single-arm phase 2 trial. *Lancet Oncol* 2016; 17:1283-94.

## **20.0 APPENDICES**

**Appendix 1 Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula**

$$\frac{\text{Creatinine Clearance (men)} = (140 - \text{Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

$$\frac{\text{Creatinine Clearance (women)} = 0.85 \times (140 - \text{Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

Reference:

Gault MH, Longenecker LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine (editorial). Nephron 1992;62:249.

**Appendix 2 Current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)**

Please use the following link to the NCI CTCAE website:

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

### Appendix 3 Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

## **Appendix 4 Anaphylaxis Precautions**

### **EQUIPMENT NEEDED**

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

### **PROCEDURES**

In the event of a suspected anaphylactic reaction during study drug infusion, the following procedures should be performed:

1. Stop the study drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observation.

**Appendix 5 Safety Reporting Fax Cover Sheet**



**GENENTECH SUPPORTED RESEARCH**

AE/SAE FAX No: (650) 225-4682

Alternate Fax No: (650) 225-5288

Page 1 of \_\_\_\_

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	
Initial Report Date	____/____/____ dd / mmm / yyyy
Follow-up Report Date	____/____/____ dd / mmm / yyyy
Patient Initials (Please enter a dash if the patient has no middle name)	____ - ____ - ____

**SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555**

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET.

## **Appendix 6 FDA MedWatch 3500 Form**

A copy of this form can be found in the link below

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM349464.pdf>